REMARKS

Claims 1 and 35 are amended to further clarify the subject matter. These amendments are supported at least by the specification at page 11, lines 21-25 and page 27, lines 5-10. Claims 9, 27, 31-33, and 42 are canceled. New claim 43 is added, as supported at least by the specification at page 11, lines 21-25.

As amended, all the claims are still readable upon the elected species. The "primate or domesticated animal" recited in claims 1 and 35 encompass the elected species of "human." The "growth factor" recited in claims 1 and 35 encompasses the elected species of "VEGF."

SEQUENCE LISTING REQUIREMENT

The Office Action contends that the RGD sequence (e.g., at pg. 37, ln. 7 of the specification) and the D-Phe-Pro-Arg chloromethyl ketone sequence (e.g., at pg. 41, ln. 8 of the specification) requires the submission of a sequence listing. Applicants respectfully submit that these two sequences are excluded from the sequence listing requirements of 37 C.F.R. § 1.821(a), which states that: "Sequences with fewer than four specifically defined nucleotides or amino acids are specifically excluded from this section." Furthermore, 37 C.F.R. § 1.821(a)(2) states: "Those amino acid sequences containing D-amino acids are not intended to be embraced by this definition." As such, Applicants respectfully submit that a sequence listing submission is not required.

REJECTIONS UNDER § 103

Independent claims 1 and 35, and various claims that depend therefrom, stand rejected under § 103(a) as being unpatentable over Naughton (US 5,830,708) in view of Vituri (Brazilian Medical Journal and Biological Research, vol. 33, pp. 889-895, 2000), Mitchell (US 2002/00115208), Patel (US 7,087,089), and Wolff (WO 99/55379). Applicants respectfully request reconsideration of this rejection.

In the method of claims 1 and 35, the body tissue of a primate or domesticated animal is conditioned (e.g., by gene transfection) *in vivo* to increase the production of a growth factor. The body tissue is harvested and decellularized to obtain an extracellular matrix material containing the growth factor. The decellularization process involves the use of a protease inhibitor.

As conceded by the Office Action, Naughton does not teach the step of conditioning body tissue of a donor animal *in vivo*. Rather, Naughton cultures and conditions tissue *in vitro*. Thus, the Office Action combines Naughton with Vituri for its teaching of altering protein levels *in vivo* in the bone marrow extracellular matrix of mice by subjecting them to malnutrition.

Claims 1 and 35 can be distinguished from Vituri in at least two ways. First, the claimed method obtains the body tissue from a primate or domesticated animal, whereas Vituri obtains the body tissue from mice. Second, the claimed method conditions body tissue for increasing the quantity of growth factors, whereas Vituri's method increases the quantity of fibronectin and laminin. Growth factors are substantially different from fibronectin and laminin. For example, fibronectin and laminin are large, structural components of the fibrous network that make up the extracellular matrix, whereas growth factors are relatively smaller proteins that are generally soluble and play a functional role in cell signaling. As Vituri readily concedes, further investigation is needed to determine whether malnutrition would have an impact on other components of the bone marrow extracellular matrix (see pg. 894, second column).

Claims 1 and 35 are further distinguished from Naughton and Vituri because neither describes decellularizing the conditioned body tissue harvested from the donor animal. As such, the Office Action further applies Mitchell and Patel for their teaching of decelluarizing body tissue harvested from animals. In the rejection of claims 13 and 30, the Office Action further applies Herlyn (WO 98/39035) for its teaching of VEGF; and in the rejection of claims 6 and 7, the Office Action further applies Schwarz (US 6,656,916) for its teaching of administering a glucocorticoid to increase the cellular expression of a gene. Without conceding that the proposed combinations of references are proper, Applicants respectfully submit that none of Mitchell, Patel, Wolff, Herlyn, or Schwarz cures the above-mentioned deficiencies of Naughton and Vituri. In summary, the combination of references suggested by the Office Action does not arrive at the claimed method.

Moreover, the claimed method is more than simply the combination of just any conditioning process, for increasing just any biologic material in the extracellular matrix, with just any decellularizing process. In the claimed method, there is a synergistic, functional relationship between the growth factor, the extracellular matrix, and the decellularizing step

using a protease inhibitor that work together to produce an extracellular matrix material having an improved ability to treat a patient's diseased or damaged body tissue.

MPEP 2141.02 instructs that a proper obviousness analysis requires a determination of "whether the claimed invention *as a whole* would have been obvious," rather than simply determining the differences between the prior art and the claims. Thus, it is improper to argue that a claim is obvious simply because each element of the claim, taken by themselves, can be found somewhere in the prior art. Applicants respectfully submit that the claimed method, as a whole, is not appreciated by the cited references.

In the claimed method, the conditioning step is for increasing the quantity of growth factors in the extracellular matrix. There is a functional relationship between these two elements of the conditioning step because the extracellular matrix can serve as a local depot for the storage of growth factors. *See*, *e.g.*, Taipale et al., "Growth factors in the extracellular matrix," FASEB Journal, vol. 11 (1997) (attached). As such, the extracellular matrix material of the present invention can provide a rapid release of growth factors into the local environment (e.g., into a wound) without the need for the time-consuming process of *de novo* protein synthesis. Thus, because the extracellular matrix can serve as a storage depot for growth factors, there is a special functional relationship in the claimed method between the growth factor and the extracellular matrix, which work together to produce an extracellular matrix material having an improved ability to treat a patient's diseased or damaged body tissue.

Moreover, the decellularizing step using a protease inhibitor works in conjunction with the increased growth factors present in the extracellular matrix. In general, these growth factors are attached to the extracellular matrix by protease-sensitive bonds. It is the proteolysis of these bonds that allows for the rapid release of the growth factors into the local environment. Therefore, during the decellularization step, proteases released from lysed or disrupted cells may cause the unwanted, premature release of the growth factors from the extracellular matrix. As a result, the growth factors would be lost from the extracellular matrix and the work performed in conditioning the body tissue to increase growth factor production would be negated. In the claimed method, the use of a protease inhibitor in the decellularizing step plays the important role of preserving the increased growth factors produced in the conditioning step.

Thus, the invention of claims 1 and 35 is more than just the sum of its parts. There is a special functional relationship between the growth factor, the extracellular matrix, and the

decellularizing step using a protease inhibitor that work synergistically together to produce an extracellular matrix material having an improved ability to treat a patient's diseased or damaged body tissue.

For at least these reasons, Applicants respectfully submit that claims 1 and 31, and the claims that depend therefrom, are non-obvious over the cited references. Accordingly, withdrawal of the rejections is respectfully requested.

Summary

The combination of references cited by the Office Action does not arrive at the claimed invention. Moreover, it is improper to argue that a claim is obvious simply because each element of the claim, taken by themselves, can be found somewhere in the prior art. MPEP 2141.02 instructs that a proper obviousness analysis requires a determination of "whether the claimed invention *as a whole* would have been obvious," rather than simply determining the differences between the prior art and the claims.

Applicants respectfully submit that the claimed invention, when viewed as a whole, is non-obvious. As a whole, the claimed method is more than simply the combination of just any conditioning process, for increasing just any biologic material in the extracellular matrix, with just any decellularizing process. In the claimed invention, there is a synergistic, functional relationship between the growth factor, the extracellular matrix, and the decellularizing step using a protease inhibitor that work together to produce an extracellular matrix material having an improved ability to treat a patient's diseased or damaged body tissue. This particular combination of functional relationships is not appreciated by the cited references.

CONCLUSION

Applicant(s) respectfully submit that the present application is in condition for allowance. The Examiner is invited to contact Applicant(s)' representative to discuss any issue that would expedite allowance of this application.

The Commissioner is authorized to charge all required fees, fees under § 1.17, or all required extension of time fees, or to credit any overpayment to Deposit Account No. 11-0600 (Kenyon & Kenyon LLP).

Respectfully submitted,

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